Proposed synopsis on

"MODIFICATIONS OF NATURAL POLYSACCHARIDE FOR DRUG DELIVERY"

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INTRODUCTION:-

Polysaccharides are polymers of simple sugar building blocks. Polysaccharides functions as thickeners, stabilizers, suspending agents, gelling agents, film formers, flocculants, binders, emulsifiers, lubricants, texturing agents and structuring agents (R. L. Whistler.1993, M. Glickman 1982,) The International Pharmaceutical Excipients Council defines excipients as "substances, other than the active drug substance of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect; support; enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use (Shireesh P. Apte 2003).

Humans have learnt through ages to exploit nature's resources in many ways from time immemorial. They used biomaterials in the form of wood, bone, skin, fibers etc., for their day today life. Many techniques were developed to modify these materials, e.g. to make leather from hides, to dye fibers, and to prepare paints and glues. Chemical modification of natural polymers began during 1800s to synthesize many new materials. The most famous of these were vulcanized rubber, gun cotton, and celluloid. The first semi-synthetic polymer produced was Bakelite in 1909 and was soon followed by the first synthetic fiber, rayon, which was developed in 1911 (www. plastics.americanchemistry.com). Though the synthetic polymers are ruling the world since World War II, the necessity to revive the use of biomaterials arises recently due to the fact that they are naturally abundant, renewable, biodegradable, cost effective and ecofriendly. Above all, biopolymers offer degree of functionality not available in most synthetic polymers. All pharmaceutical dosage forms contain many additives besides the active ingredients to assist manufacturing and to obtain the desired effect of the pharmaceutical active ingredients. The advances in drug delivery have simultaneously urged the discovery of novel excipients which are safe and fulfill specific functions and directly or indirectly influence the rate and extent of release and /or absorption. The plant derived gums and mucilage's comply with many requirements of pharmaceutical excipients as they are non-toxic, stable, easily available, associated with less regulatory issues as compared to their synthetic counterpart and inexpensive;

also these can be easily modified to meet the specific need. Most of these plant derived gums and mucilage's are hydrophilic and gel- forming in nature. Recent trend towards the use of plant based and natural products demands the replacement of synthetic additives with natural ones..

Polysaccharides are polymers of simple sugar building blocks; they are made by repeated units of monomer which are same or different. Polysaccharides made by same monomer called as homo-polysaccharide and after hydrolysis of polysaccharide as different monomer obtained called as hetero-polysaccharide. Polysaccharides functions as thickeners, stabilizers, Disintegrants, suspending agents, gelling agents, film formers, aerating agents, binder flocculants, coating former, viscosity enhancer, emulsifiers, lubricants, texturing agents and structuring agents. (Whistler RL *et al* 1993, Glickman M.1981) in the manufacture of solid monolithic matrix, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations (Alonso-Sande et al 2008, Chamarthy, S.P and Pinal, R 2008) Due to advances in drug delivery technology, excipient are currently included in novel dosage forms to fulfill specific functions, directly or indirectly influence the extent as well as rate of drug release and absorption. Since plant Polysaccharide comply with requirements expected of pharmaceutical excipient such as non-toxicity, physically and chemically modification, stability, availability plant resources are renewable and if cultivated or harvested in a sustainable manner. Polysaccharides are primarily used to thicken or gel water and are frequently classified into two groups thickeners and gelling agents (D. A. Rees 1967) Gelling agents are more difficult to use than thickeners and their use is complicated by the fact each requires its own set of procedure to produce satisfactory gel Thus polysaccharides are hydrated in an aqueous environment thereby creating the gel structure called hydrogel. Aqueous solutions of hydrophilic polymers at low or moderate concentrations, where no substantial entanglement of chains occurs, normally show Newtonian behavior. On the other hand, once crosslinking between different polymer chains are introduced, the so obtained network shows visco-elastic and sometimes pure elastic behavior. As the term implies, crosslink's have to be present to avoid dissolution of hydrophilic polymer chains into aqueous phase (N.A. Peppas 1986)

Over the last one decade, interest in the naturally available class of polymers known as polysaccharides (Starch, cellulose, and chitin) has been increasing rapidly, because it is a renewable resource with a wide range of uses in nature, functioning as energy storage, transport,

signaling, and structural components (Finkenstadt, 2005). In recent years, natural polysaccharides are growing rapidly importance in the new formulation development of the controlled released dosage form as they are much safer than synthetic. Interest in gums and mucilage's used in pharmaceutical industry as an excipient in various formulations for various roles such as binder, matrix former, emulsifying agent, suspending agent, floating agent, Mucoadhesive etc. (GK Jani *et al* 2007). Nature has provided us a wide variety of materials to help improve and sustain the health of all living things either directly or indirectly. In recent years there have been important developments in different dosage forms for existing and newly designed drugs and natural products, and semi-synthetic as well as synthetic excipients often need to be used for a variety of purposes. Gums and mucilage's (polysaccharides) are widely used natural materials for conventional and novel dosage forms. Mucilage is normal product of plant metabolism, produced inside the cell of plant. They are slimy masses with water, but not dissolved. Mucilage is esters of sulphuric acid. These natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and widely available. They can also be modified in different ways to obtain tailor-made materials for drug delivery systems and thus can compete with the available synthetic excipients. (Girish k Jani *et al* 2009). Since they (gums and mucilages) they are deteriorate when stored, especially in warm weather preservatives are added, such as solutions of formaldehyde or benzoic acid

Natural gums can also be modified to have tailor-made materials for drug delivery systems.(Bhardwaj T.R et al 2000) Therefore, in the years to come, there is going to be continued interest in the natural gums and their modifications with the aim to have better materials for drug delivery systems .Several polysaccharides such as sodium alginate, chitosan, guar gum, xanthan gum, pectin, gellan gum have been employed either alone or in combination with their native or modified forms to control the drug release from different types of delivery system, but these just had a limited degree of success. In recent years, graft copolymers designed primarily for medical applications have entered the arena of controlled release. (Nawaz Mahammed *et al* 2011) Chitosan, the deacetylated form of chitin, is a basic polysaccharide that is easily prepared from the shells of crabs, shrimp and prawns. Furthermore, it is an environmentally benign compound.

Chemical and physical methods are used for cross linking of polysaccharides. In physical cross linking dissolution is prevented by physical interaction which exists between different polymer chains and a molecular interaction between polymers can be achieved by exposure to dry heat, saturated steam, microwave technology, UV (N. Vatanasuchart et al 2005, A.K. Mubarak et al 2006) and gamma radiation. (G.D. Kashappa and J.P. Hyun 2006) In chemical cross linking covalent bonds are present between different polymer chains.

Techniques employed for the modification of polysaccharides :-

1) Physical Modification
    a) Physical Crosslinking
    b) Microwave modification
2) Chemical Modification
    a) Carboxymethylation
    b) Chemical Crosslinking
    c) Grafting
    d) Curing
    e) Blending etc

OBJECTIVE:

Literature survey reviles that the extensive efforts have been made in pharmaceutical research laboratories for the development and modification of natural polysaccharide by various chemical and physical modification methods. In the light of above fact and literature survey the objective of our study was design with following objectives.

- To perform Pilot study for selection of natural polysaccharide
- To evaluate natural polysaccharide by various tests and analytical techniques.
- To test natural polysaccharide for drug delivery.
- To compare performances of natural polysaccharide with synthetic polymer.
- To modify natural polysaccharide by various physical and chemical methods.

- To evaluate the modified polysaccharide by various test and analytical techniques.
- Formulation and development by using modified natural polysaccharide.
- Stability study.
- To obtain in vivo study of best formulation.

Plan of Work:-

Part I

1. Extensive literature survey
2. Pilot study for selection of natural polysaccharide.
3. Authentification of plant.
4. Procurement of Drug and Excipient
5. Preformulation studies of Drug and excipient

Part II

1. Extraction
2. Evaluation of obtained natural polysaccharide.
    a. Preliminary tests
    b. Phytochemical Analysis
    c. Analytical tests:
        UV spectroscopy
        Infrared spectroscopy
        Mass spectroscopy
        Nuclear magnetic resonance spectroscopy
        Differential scanning calorimetry.
3. Test obtained polysaccharide as drug delivery carrier (agent).
4. Compare performances of natural polysaccharide with synthetic agent.
5. Modify polysaccharide by physical and chemical modification methods.
6. Evaluate the modified polysaccharide by various test and analytical methods.
    - Preliminary tests
    - Phytochemical Analysis

- Analytical tests:
    - UV spectroscopy
    - Infrared spectroscopy
    - Mass spectroscopy
    - Nuclear magnetic resonance spectroscopy
    - Differential scanning calorimetry.

Part III

1. Formulation and development of dosage form by using modified polysaccharide.
2. Compare formulation using natural polysaccharide and modified polysaccharide.
3. Stability study.

REVIEW OF LITERATURE:-

Lenaerts V. *et al* (1998), Cross-linked high amylose starches have been developed as suitable excipients for controlled release solid oral dosage forms with high loading capacities of active ingredient and with the capability of achieving quasi-zero order release for most drugs. Other advantages include absence of erosion, limited swelling and the ability to control the rate of drug release by changing the degree of cross-linking

Dale L. Munday *et al* (2000), prepared directly compressed matrices containing either xanthan gum or karaya gum as a release-controlling agent. These swellable hydrophilic natural gums were used to control the release of varying proportions of two model drugs, caffeine and diclofenac sodium, which have different solubilities in aqueous medium. Gum erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method) at two agitation speeds. Xanthan gum displayed a high degree of swelling due to water uptake and a small degree of erosion due to polymer relaxation. Neither agitation speed nor drug solubility had any significant effect on water uptake, but matrices with the lower proportion of gum produced a lesser degree of hydration. In contrast, karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed. Drug release from xanthan and karaya gum matrices depended on agitation speed, solubility and proportion of

drug. Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices.

Krishnaiah Y.S.R, *et al* (2002), designed oral controlled drug delivery for highly water-soluble drugs using guar gum as a carrier in the form of a three-layer matrix tablet. Metoprolol tartrate was chosen as a model drug due to its high water solubility. Matrix tablets containing either 30 (M1), 40 (M2) or 50% (M3) of guar gum were prepared by wet granulation technique using starch paste as a binder. Three-layer matrix tablets of metoprolol tartrate were prepared by compressing on both sides of guar gum matrix tablet granules of metoprolol tartrate M1,M2 or M3 with either 50 (TL1M1, TL1M2 or TL1M3) or 75 mg (TL2M1, TL2M2 or TL2M3) of guar gum granules as release retardant layers. Both the matrix and three-layer matrix tablets were evaluated for hardness, thickness, drug content uniformity, and in vitro drug release studies. The amount of metoprolol tartrate released from the matrix and three-layer matrix tablets at different time intervals was estimated by using a HPLC method. Matrix tablets of metoprolol tartrate were unable to provide the required drug release rate. However, the three-layer guar gum matrix tablets (TL2M3) provided the required release rate on par with the theoretical release rate for metoprolol tartrate formulations meant for twice daily administration. The three-layer guar gum matrix tablet (TL2M3) showed no change either in physical appearance, drug content or in dissolution pattern after storage at 40 °C/75% RH for 6 months.

Zohuriaan-Mehr *et al* (2003), modified various natural polysaccharides (*i.e.* arabic gum, tragacant gum, xanthan gum, sodium alginate, chitosan, sodium carboxymethyl cellulose, hydroxyethyl cellulose, methyl cellulose) using ceric-ions as initiator of acrylonitrile graft under inert atmosphere. They pointed out that polyacrylonitrile-grafted polysaccharides were thermally more stable than the corresponding nongrafted substrates. Potassium persulphate (KPS)-initiated graft copolymerization of acrylonitrile and methylmethacrylate onto chitosan has been reported. A maximum graft yield of 249% was obtained with 0.12 M of acrylonitrile and 0.00074 M of KPS at 65°C for 2 h for 1% chitosan solution. For chitosan-*g*polymethylmethacrylate, 0.14 M of methylmethacrylate at 65°C gave a maximum grafting of 276%. No residual monomers were found by HPLC in the graft copolymers.

Bravo S. A. *et al* (2004), to evaluate the effects of HPMC and carboxy polymer (carbopol 934) on the release behaviour of Diclofenac sodium from a swellable matrix tablet system. The influence of the polymer content, the polymer ratio, the polymeric swelling behavior and the pH changes on the release rate of Diclofenac sodium was investigated. There was no significant difference in drug release when total polymer concentration was 10%. When the tablets were formulated having 20% or 30% of HPMC/cabomer, it was observed that a more rapid release of Diclofenac sodium occurred as carboxy polymer ratio within the matrices increased.

Jian Du *et al* (2004), Prepared Nanoparticals by cross-linking Carboxymethyl Konjac Glucomannan and Chitosan (CKGM-CS). Their study showed that the nanoparticulate system driven by complex formation has potential as an advanced drug-delivery system for water-soluble drugs.

Sung-Ching Chen *et al* (2004), Developed pH-sensitive hydrogel system composed of a water-soluble chitosan derivative (*N*,*O*-carboxymethyl chitosan, NOCC) and alginate blended with genipin for controlling protein drug delivery. Swelling characteristics of these hydrogels as a function of pH values were investigated. Additionally, release profiles of a model protein drug (bovine serum albumin, BSA) from test hydrogels were studied in simulated gastric and intestinal media. Their results clearly suggested that the genipin-cross-linked NOCC/alginate hydrogel could be a suitable polymeric carrier for site-specific protein drug delivery in the intestine.

Nande, V.S. (2006), Derivatives of rosin synthesized by a reaction with polyethylene glycol 200 and maleic anhydride proofed suitable for sustaining drug release from matrix tablets and pellets.

Varshosaz J. *et al.* (2006), developed matrix sustained-release tablets of highly water-soluble tramadol HCl using natural gums (xanthan and guar gum) compared with the extensively investigated hydrophilic matrices [HPMC, CMC]. Different ratios of 100:0, 80:20, 60:40, 20:80, 0:100 of G gum (or X): HPMC, X gum:G gum, and triple mixture of these polymers (G gum, X

gum, HPMC) were applied. Tablets with only X had the highest Mean Dissolution Time (MDT), the least dissolution efficiency (DE), and released the drug following a zero-order model via swelling, diffusion, and erosion mechanisms. Guar gum alone could not efficiently control the drug release, while X and all combinations of natural gums with HPMC could retard tramadol HCl release. However, according to the similarity factor (f_2), pure HPMC and H_8G_2 were the most similar formulations to Topalgic-LP as the reference standard.

Anuradha Mishra *et al.* (2007), Synthesis and characterization of *Okra* mucilage, *Okra* gum has been modified by grafting acrylamide (AAm) for developing the new green polymeric materials. Grafting has been done under N_2 atmosphere using redox initiator and hydrogels were prepared by using N,N-methylenebisacrylamide (NN-MBAAm) as crosslinker. The effect of monomer concentration, initiator concentration, reaction time and temperature in terms of grafting efficiency (%GE), percent grafting (PG) and percent gel (%G) has been investigated. The grafted polymers and hydrogels were characterized by SEM, XRD and FTIR techniques to study various structural aspects. The swelling behavior of the crosslinked polymeric material has also been studied as a function of time, temperature and pH. Higher is the concentration of ceric ions then length of grafted chains will be larger, as lower the ceric ion concentration the grafted chain length should be shorter. *Okra* mucilage and *Okra*-cl-poly(AAm) show an amorphous nature While *Okra* grafted by *Okra*-g-poly(AAm) showed crystalline peak.

Jani, G.K.*et al* (2007), Extraction of the *Alove vera* gel from the leaves of *Aloe Barbadensis* Miller and a filtration step, then gel was treated with acetone, precipitate mucilage was dried and used for directly compressed in matrix systems with diclofenac sodium as model drug. The mucilage produced direct compressible matrix tablets that showed good swelling and sustained release of the model drug.

Manish S. Bhatia *et al* (2008), Chemical Modification of Pectin was done by limited acetylation of their free hydroxyl groups to yield high ester pectin and to investigate its swelling and erosion behaviour along with the effect on the release pattern of drugs. Ibuprofen as a weakly acidic drug was formulated as tablets using chemically modified pectin and its impact on drug release was

studied. Optimum concentrations of the modified pectin in such a system protect the tablet throughout the gastrointestinal tract (GIT) for 10–12 hrs. The pectin modified with acetylating agent was found to be promising to modify the release of drugs which are to be delivered throughout GIT. Drug dissolution studies were carried out in buffers of pH 1.2 and 6.8 and the system was designed based on the total GIT transit time concept. This article reviews physicochemical characterization of chemically modified pectin, correlation of the physicochemical characteristics with the drug release pattern of ibuprofen and the potential use of chemically modified pectin for modified release dosage forms.

Dhiren p. Shah, Girish k. Jani (2009), Gellan gum was modified by physical method. Modifying temperature is one of the most favour approaches for modification. gellan gum was modified by microwave technology and compared its various physicochemical properties with those of pure gellan gum. Confirmation of physical modification was carried out with differential scanning calorimetry (DSC) and X-ray diffractomy. Chemical changes in the modified material were analyzed with Fourier transfer infrared (FT-IR) spectroscopy. Optimization of the amount of distilled water and time of exposure in microwave was carried out using a 3^2 full-factorial design. Tablets of lactose and dibasic calcium phosphate that also contained modified gellan gum were prepared, and the effect on tablet disintegration time, hardness, and friability were measured. Amount of distilled water taken 60, 70 and 80ml while time of expose in microwave were 8, 10 and 12 minutes. Pure Gellen gum possesses high viscosity and gelling ability, which can be useful as release retardants in the preparation of a controlled-release formulation. The viscosity of pure gellen gum was reduced when it was exposed to high temperature. Hence, a modified form was prepared by exposing pure gellen gum in a microwave oven at higher temperature for different time periods. The results of physical changes attributed to pure gellen gum upon modification shows a marked decrease in viscosity as well as gelling ability. The Modified gellen gum possesses excellent swelling property but lesser viscosity. X-ray diffraction revealed that there was a change of nature from amorphous to crystalline. Modified gellen gum was explored as a Disintegrating agent in tablet formulation.

Federica Corrente *et al* (2009), synthesized carboxymethyl derivative of scleroglucan (Scl-CM) with a 65±5% carboxylic group degree of derivatization (DD). By an appropriate combination of

the hydrogels prepared using different amounts of salt, it was possible to obtain a system able to release diclofenac with zero-order kinetics.

Their results suggest a potential of the new hydrogels for the development of modified topical drug delivery systems.

Ashwini rajendra and Bushetti S.S *et al* (2012), development of polyelectrolyte matrix tablets using *Okra* and chitosan as natural polymers, Okra-chitosan Complex has maximum yield (96.4%) at pH 5 and polymer volume ratio was 9:1 for *Okra*:chitosan. Characterization of complex by FT-IR, DSC etc. matrix tablets were formulated using different drug:polymer ratios. Interaction should be takes place among the amino group of chitosan and carboxyl group of Okra polysaccharide. In vitro Drug release study was carried out in pH 6.8 phosphate buffer solution, f2 and f3 formulations show extended release at 8hr. 83.87% and 77.12% respectively.

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